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Research Article

The Role of Cholinergic Receptors in the Implementation of the Stimulating Effect of Serotonin on the Stomach

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Abstract

The aim of the study: Was to elucidate the role of cholinergic receptors in the stimulating effect of serotonin on gastric motility.

Materials and methods: The studies were performed on sexually mature Wistar rats on an empty stomach under the conditions of the whole organism in the surgical stage of anesthesia (nembutal, 60 mg/kg intramuscularly). The electromyogram and hydrostatic-pressure in the gastric cavity were recorded using the BioAmp ML132 amplifier (Adinstruments, Australia), the Maclab 8e analog-to-digital converter (Adinstruments, Australia), the Macintosh Performa 6400/180 computer and the Chart 4.2.3 program.

Results and Discussion: It was found that the preliminary blockade of N-choli noreceptors leads to an increase in the stimulating effect of the stomach on the introduction of serotonin by 40%, in conditions of blockade of M-cholinergic receptors - by 56%. The blockade of N-cholinergic receptors itself increased the strength of gastric contractions by 32%, while a separate blockade of M-cholinergic receptors was not accompanied by a change in the strength of gastric contractions.

Conclusion: The weakening of the stimulating effect of serotonin on gastric motility with the help of N- and M-cholinergic receptors is carried out through the activation of adrengic and VIPergic inhibitory neurons.

Keywords: Stomach; Motility; Serotonin; M- and N-cholinergic receptors

Abbreviations

5th receptors: Five Hydroxytryptamine (Serotonin) Receptors, Myogram: Hydrostatic Pressure in the Stomach Cavity; EMG: Electromyogram; ANS: Autonomic (Autonomous) Nervous System; VIP" Vasoactive Intestinal Peptide

Introduction

The effect of serotonin on smooth muscle contractions of internal organs has been studied in animal experiments and in patient studies. Thus, [1] in experiments on anesthetized non-sensitized guinea pigs, it was shown that intravenous administration of serotonin dose-dependently affects pulmonary resistance. This means that serotonin causes bronchospasm.

According to other researchers, serotonin increases gastric motility in guinea pigs [2] and in rabbits [3]. In experiments on rats, it was shown [4] that the 5HT agonist of mozapride 4-receptor citrate (mosapride citrate) is able to enhance gastric motility when administered intraperitoneally.

Studies on fasting patients with the use of serotonin were performed [5]. They recorded the myoelectric activity of the gastrointestinal tract using the GASTRON-1 electro gastro

intestinograph (Russia). This device provides reception and registration of signals using skin electrodes, as well as storage, processing and documentation of the information received. All patients under local anesthesia were fitted with an endolymphatic catheter in the inguinal catheter lymph node on the right. With the help of a syringe pump «DSh-08» carried out the infusion of the drug serotonin adipate at a dose of 10 mg once. V 1 hour after endolymphatic infusion and after 8 hours the amount of serotonin in the serum of patients was within normal limits. Within 3-7 hours, patients had the discharge of intestinal gases and the appearance of independent stools [5]. These authors believe that endolymphatic infusion of serotonin adipate is an effective tool in the fight against postoperative intestinal paresis. Allergic reactions and adverse effects on the administration of the drug were not noted.

However, the possible role of cholinergic receptors in the implementation of the stimulating effect of serotonin on smooth muscles has not been studied. Knowledge of these mechanisms is important both for scientific research and for practical medicine, since serotonin is used for therapeutic purposes. It is known that intestinal paresis is a frequent and dangerous complication in elderly patients, leading to acute intestinal obstruction.

Materials and Methods

Our experiments were performed on 35 sexually mature Wistar rats of both sexes, weighing 250-450g. Studies were carried out on animals on an empty stomach (12 hours after eating) under conditions of the surgical stage of anesthesia (nembutal 60 mg/kg intramuscularly). During the experiments, the average duration of which was 2.5 hours, anesthesia was sufficient and passed without complications. Before the experiment, three rats were kept in one on the basis of the hydrostatic pressure in its cavity (recorded using a catheter) and the EMG of the longitudinal layer of smooth muscles (recorded using an electrode). Signals from the catheter and electrode were fed to the BioAmp ML132 amplifier (Ad instruments, Australia), then to the Maclab 8e analog-to-digital converter (Ad instruments, Australia), connected After checking the data for normality, statistical processing was carried out using the paired Student's test, taking $p < 0.05$ as the significance level. Serotonin adipate (0.1 mg/kg) was administered intraarterially, since in the first (trial) experiments we found an unexpected result - intravenous administration of various doses of serotonin Adipate (up to 20mg/kg) did not increase the contraction of the stomach. The use of large doses of a mediator or hormone in the experiment devalues the results obtained. In addition, with intra-arterial administration of serotonin, its influence from the reflexogenic zones of the pulmonary circulation on the results obtained is excluded. Possible reflex effects of serotonin on motility the stomach in our experiments was prevented by bilateral intersection of the vagus and glossopharyngeal nerves in the neck.

Thus, the use of our experimental approaches limits the effect of cerotoninon systemic blood flow, and the parallel registration of the myogram and EM G increases the reliability of the results obtained. Serotonin was administered in a volume of 0.1 ml for 30s.

Results and Discussion

In the first series of experiments, we studied whether the role of N-cholinergic receptors in the implementation of stim ulatory effects of serotonin. E experiments were performed on 15 animals. 15 reactions of the stomach to the introduction of serotonin into the body, and before the blockade of N-cholinergic receptors and 15 reactions against the background of the action of pentamine, an N-cholinergic receptor blocker, were recorded. In figure 1. The reaction of the stomach to the blockade is shown N-cholinergic receptors prior to the administration of serotonin.

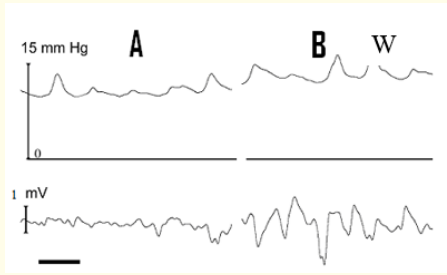

Figure 1: Strengthening the contractions of the rat's stomach for the introduction of pentamine into the body - a blocker of N-cholinergic receptors: A - background before the introduction of pentamine; B - 10 minutes after the administration of pentamine; at the top - myogram; at the bottom - EMG; a short horizontal line at the bottom is a mark of pentamine administration (30 s).

The total results of the first series of experiments showed that the shutdown of N-cholinergic receptors of the autonomic ganglia led to a significant increase in gastric contractions (Table 1).

The introduction of serotonin 10 minutes after the injection of N-anticholinergic blocker in all 15 animals caused stronger stimulic responses than with intact N-cholinergic receptors (see Table 1 and Figure 2). This means that intact N-cholinergic receptors interfere with the stimulating effect of serotonin.

Anticholinergic blockers	Background before the introduction of anticholinergic blockers	The result on the introduction of anticholinergic blockers	Results on the administration of serotonin in intact animals	The result on the introduction of serotonin against the background of the action of anticholinergic blockers
Pentamin - N-anticholinergic blocker	10,2 ± 2,3	13,5 ± 2,1, (+32%), P < 0.02	Increase in pressure by 26% P < 0,02	18,9 ± 1,7; (+40%) P < 0,02
Buskopan - M-cholinoblokator	10,9 ± 2,9	11,0 ± 1,9, (+1%) p > 0,05	Increase in pressure by 26% P < 0,02	17,2 ± 2,2; (+56%) P < 0,01

Table 1: Increase in hydrostatic pressure in the stomach cavity of rats (mm Hg and %) after intra-arterial administration of serotonin under various conditions.

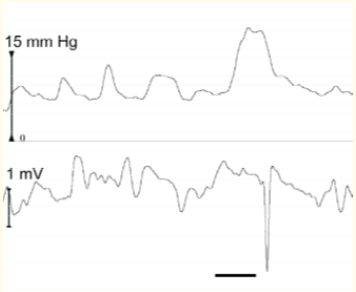

Figure 2: Increased contractions of the stomach (myogram) after the introduction of serotonin into the body against the background of the action of the N-anticholinergic blocker pentamine; a short horizontal line at the bottom is a mark of serotonin administration (30 s).

The electrical activity on the introduction of serotonin, according to the entire series of experiments, practically did not change.

In the second series of experiments, the role of M-cholinergic receptors in the implementation of the stimulating effect of serotonin was investigated. In experiments on 13 animals, it was first established that buscopan (1 mg/kg, subcutaneously) does not affect the background motility of the stomach (see Table 1).

Further in the same experiment after 10 minutes. Against the background of the continued action of buscopan, serotonin (0.1 mg/kg) was injected into the body. In all 13 animals, pronounced stimulant reactions were observed (see table 1 and figure 3), electrical activity also increased, from 0.72 ± 0.45 to 1.2 ± 0.23 mV (+ 67%, $p < 0.01$, see Figure 3).

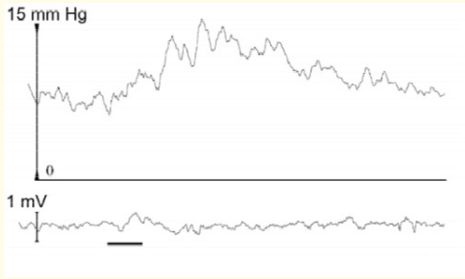

Figure 3: The reaction of the stomach to the introduction of serotonin into the body against the background of the action of the M-anticholinergic blocker buscopan: at the top - myogram; at the bottom - EMG; a short horizontal line at the bottom is a mark of serotonin administration (30 s).

In the reliability of the blockade of M-cholinergic receptors using a dose of buscapan (1 mg/kg), we were convinced in control experiments on 7 rats with irritation of the peripheral segment of the right vagus nerve with rectangular pulses of 1 mA, 10 Hz, 1.5 ms. In all 7 animals, stimulant reactions were noted before the introduction of buscopan: hydrostatic pressure in the stomach increased from 10.9 ± 2.54 to 15.56 ± 2.58 mm Hg, (+ 43%, $p < 0.02$), electrical activity also increased (from 0.72 ± 0.43 to 1.23 ± 0.18 mV), (+71%, $p < 0.01$), Figure 4 A Repeated stimulation of the vagus nerve 10 minutes after the administration of buscopan was not accompanied by increased gastric contractions (see Figure 4B).

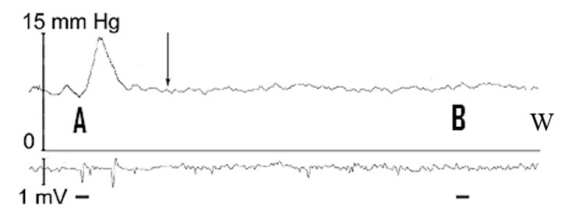

Figure 4: Stimulant reaction of the rat stomach to irritation of the right vagus nerve in intact animals (A) and its shutdown by buscopan (B): at the top - myogram; at the bottom - EMG; short horizontal lines at the bottom - nerve stimulation marks (30 s), arrow - the moment of introduction of buscopan.

We draw the reader's attention to the strong contractions of the stomach with a weak short-term increase in EMG after eating serotonin (see figure 3). This means that the evaluation of the mechanical activity of a hollow smooth muscle body by recording the hydrostatic pressure of modern electronic equipment in its cavity is a more reliable technique than electromyography.

The average duration of stimulant reactions to serotonin under conditions of blockade of N-cholinergic receptors was 156 + 16s, M-cholinergic receptors 206 + 32s, in intact animals 146 ± 45s.

Discussion of the Results

Thus, the blockade of M- and N-cholinergic receptors leads to an increase in the stimulant effects of the stomach on the introduction of serotonin into the body. This indicates that intactnye M- and N-cholinergic receptors interfere with the action of serotonin. The question arises - what is the mechanism of this phenomenon**?**

Mechanism Andit is known [6,7] that the preganglionic nerve fibers of the vagus nerve form synapses with ganglionic inhibitory VIP and excitatory cholinergic neurons with the help of N-cholinergic receptors, and preganglionic sympathetic fibers with inhibitory adrenergic by neurons, also with the help of N-cholinergic receptors (Figure 5).

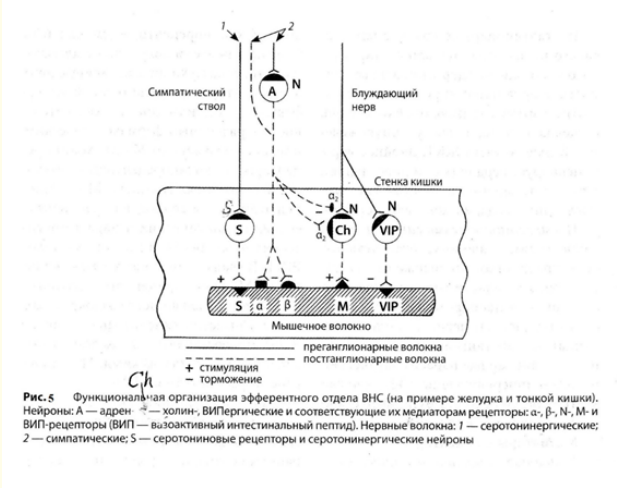

Рис. 5 Функциональная организация эфферентного отдела ВНС (на примере желудка и тонкой кишки). Нейроны: А — адрен- , Ch — холин-, ВИПергические и соответствующие их медиаторам рецепторы: α-, β-, N-, M- и ВИП-рецепторы (ВИП — вазоактивный интестинальный пептид). Нервные волокна: *1* — серотонинергические; *2* — симпатические; S — серотониновые рецепторы и серотонинергические нейроны

Figure 5

Preganglionic serotonergic fibers form synapses with ganglionic excitatory serotonergic neurons, the postganglionic fibers of which excite gastric myocytes [7,8], see figure 5.

From this it follows that the excitatory effect of serotonin with intact all of these receptors on gastric contractions is carried out by activating the serotonergic nerve pathway [7,8], see Fig. 5 and activating serotonin receptors in gastric myocytes, the presence of which has been established by other researchers and [9,10], as well as with by activating presynaptic serotonin receptors of parasympathetic terminals, the presence of which has been established [11,12]. At the same time, the acetylcholine they release stimulates stomach contractions.

The inhibitory effect on the action of serotonin in intact N-cholinergic receptors is realized by activating inhibitory adrengic and VIP-ergic neurons. This is done by excitation of presynaptic serotonin receptors of the endings of preganglionic cholinergic nerve fibers and their release of acetylcholine, which excites inhibitory adrenic and VIP-ergic neurons (see figure 5).

Themechanism of weakening the stimulating effect of serotonin on gastric contraction with the help of M-cholinergic receptors has not yet been sufficiently studied, but this fact, from our point of view, is very important, since serotonin is beginning to be used in clinical practice for the treatment of constipation [5,13]. We believe that when M-cholinergic receptors are activated, inhibitory adrenic and VIP-ergic neurons, which weakens the excitatory effect of serotonin. The presence of other inhibitory neurons in the stomach and in the autonomic ganglia has not been established [6,7].

Tonic action of autonomic nerves

The tone of the vagus nerve for the stomach is not expressed. This is evidenced by the fact that the blockade of excitatory M-cholinergic receptors of the stomach does not change the strength of its contractions (see Table 1).

The inhibitory tone of thesympathetic nerve for the stomach is *well expressed*, which is proved by the strengthening of the coloring of the stomach after the blockade of this nerve with pentamine. At the same time, the vagus nerve is also turned off, but it does not have a tone for the stomach, therefore it does not participate in changing the motor activity of the organ during the blockade of N-cholinergic receptors. The tone of the serotonergic nerve has not been sufficiently studied.

Conclusion

The weakening of the stimulating effect of serotonin on gastric motility with the help of N- and M-cholinergic receptors is carried out through the activation of adrengic and VIPergic inhibitory neurons.

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